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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ARNOLD & PORTER
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EXAMINER	
BAUM, STUART F	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,992	BORONAT ET AL.	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/21/2003, 7/25/2003, 10/23/2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *6 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

9/5/03

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 8/29/03
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2/13/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-10 are pending.

2. Applicant's election with traverse of Group I claims 1-5 and 7-9 including SEQ ID NO:3 and 50 in Paper No. 8 and 10 filed 4/20/2003 and 7/25/2003, respectively, and the election response filed 10/23/2003 is acknowledged. The traversal is on the ground(s) that the three groups can be searched and examined without creating a serious burden to the Examiner. Also, Applicants contend that searching all sequences would not create a serious burden for the Examiner. Applicants continue by stating the MPEP states that "up to 10 independent and distinct nucleotide sequences will be examined in a single application" (page 3, 2nd paragraph of paper filed 4/18/2003). In addition, Applicants believe that the claims of Group III are drawn to a species of the genus claimed in claim 9. In particular, Applicants contend that Groups I and III, drawn to plants transformed with nucleic acid sequences in sense or antisense orientation should be examined together. Lastly, because Groups I and III are classified in the same class and subclass, the Groups should be examined together.

This is not found persuasive because even for groups classified in the same class and subclass, the search of the prior art for one group may overlap with that of another, they are not co-extensive of each other and thus would be a burden on the Office. In regards to the permissible number of sequences as specified in the MPEP, those guidelines were for EST sequences which are much shorter than the nucleic acid sequences presented in the present application, and because of the vast number of sequences now present in the current databases that must be searched, the office does not have the resources to search more than one corresponding pair of nucleic acid and amino acid sequences per application. And lastly,

according to the MPEP, up to ten sequences will be examined, and one sequence is considered up to ten, for the reasons stated above.

Applicants are claiming a nucleic acid molecule in sense and antisense orientation. It is recognized in the art, that nucleic acid molecules in antisense orientation are used to down-regulate the expression or reduce the activity of a specific protein whereas over-expressing a nucleic acid molecule in sense orientation is used to upregulate or increase the activity of a specific protein. The two different sequences, i.e., antisense and sense, utilize different mechanism and therefore require an independent search and examination.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6 and 10 are withdrawn from consideration as they are drawn to non-elected inventions.

3. Claims 1-5 and 7-9 are examined in the present office action.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See for example page 91, line 17; page 100, line 17; page 108, line 9. See MPEP § 608.01.

Drawings

5. The drawings are objected to because Figure 5 has text that is not discernable and Figure 2 is missing. Correction is required.

Claim Objections

6. Claims 1, 3, 4, and 9 are objected to for reading on non-elected inventions. Correction is required.

Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 3 is objected to for reciting "identity" instead of "sequence identity".

Claim 9 is objected to for improper grammar. In line 1, it is suggested that Applicant either insert "a" before the recitation "seed" or replace the recitation "seed" with --seeds--.

Claim 9 is objected to for reciting an improper article. On line 2, the recitation "the" should be replaced with --a--.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 2, the recitation "peptide-encoding sequence" is unclear. As worded, the claim reads on a protein that is operably linked to a nucleic acid sequence encoding a transit peptide. Deleting the words "-encoding sequence" will obviate the rejection.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to an isolated nucleic acid molecule that hybridizes under moderate stringency conditions to SEQ ID NO:3 or an isolated nucleic acid sequence that exhibits greater than 85% identity to SEQ ID NO:3.

Applicants disclose the E. coli gcpE nucleic acid sequence of SEQ ID NO:3 encoding 1-deoxy-D-xylulose 5-phosphate reductoisomerase of SEQ ID NO:50.

Applicants do not identify structural features unique to the E. coli 1-deoxy-D-xylulose 5-phosphate reductoisomerase protein, nor the functional domains of the protein. The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Given the lack of description for the E. coli 1-deoxy-D-xylulose 5-phosphate reductoisomerase protein, it remains unclear what features identify an E. coli 1-deoxy-D-xylulose 5-phosphate reductoisomerase protein, including a E. coli 1-deoxy-D-xylulose 5-phosphate reductoisomerase encoding nucleic acid that hybridizes under moderate stringency to SEQ ID NO:3. Since an E. coli 1-deoxy-D-xylulose 5-phosphate reductoisomerase protein has not been described by specific structural features, the specification fails to provide an adequate written description to support the generic claims.

Sequences that hybridize under moderate stringency with SEQ ID NO:3 or that exhibit 85% identity to SEQ ID NO:3 encompass naturally occurring allelic variants, mutants of the E. coli 1-deoxy-D-xylulose 5-phosphate reductoisomerase protein, as well as sequences encoding proteins having no known 1-deoxy-D-xylulose 5-phosphate reductoisomerase activity, of which Applicant is not in possession. Absent of such disclosure, one skilled in the art cannot determine

the genus of sequences based upon the disclosure of the sequence of SEQ ID NO:3 with any certainty or predictability. Accordingly, the specification fails to provide an adequate written description to support the hybridization language or percent identity language as set forth in the claims. (See Written Description guidelines published in Federal Register/Vol. 66, No.4/Friday, January 5, 2001/Notices: p.1099-1111).

Enablement

9. Claims 1-5, 7-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a nucleic acid molecule encoding an amino acid sequence of SEQ ID NO:50, said nucleic acid molecule comprising a promoter, a cell or plant transformed therewith, a nucleic acid molecule that hybridizes under moderate stringency conditions to SEQ ID NO:3 or a method of producing a transgenic plant having seeds with altered isoprenoid compound levels comprising transforming a plant with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:50.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or

absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

Applicants cloned the *gcpE* nucleic acid from E. coli, wherein said nucleic acid encodes 1-deoxy-D-xylulose 5-phosphate reductoisomerase (dxr), which catalyses the first committed step of the methyl-D-erythritol phosphate (MEP) pathway (page 91, top paragraph). Applicants subcloned the *gcpE* nucleic acid into a binary vector which was subsequently transformed into Agrobacterium that was then used to transform Arabidopsis (pages 103-107).

Applicants fail to disclose how one skilled in the art would use a plant transformed with the gcpE nucleic acid given that Applicants do not report any differences in protein levels associated with the MEP pathway or any products produced from the MEP pathway nor do Applicants report any alteration in isoprenoid compound levels.

Applicants purport that overexpressing the *gcpE* nucleic acid will alter the isoprenoid compound levels in seeds. But, Applicants have not reduced to practice their invention. Altering isoprenoid compound levels is a complex, highly regulated process involving multiple proteins in multiple pathways. Applicants' own admitted statement that there exists many different isoprenoid compounds whose biochemical pathways are interconnected (page 3, second paragraph). It is highly unlikely that one protein controls the concentration of isoprenoid compounds. More likely, there are multiple proteins with redundant functions that are involved in the process to ensure that isoprenoid compounds are produced at the required concentrations. Applicants' own admitted statement that IPP is a central intermediate in the production of isoprenoids and that two pathways exist to generate IPP (page 4, second full paragraph). In

addition, if isoprenoid biosynthesis was controlled by a single protein, then mutagenesis experiments should have already uncovered the gene responsible for encoding this protein. But to date, no such gene has been uncovered by chemical or insertional mutageneses. Applicants have not shown that *gcpE* alone can regulate or control isoprenoid biosynthesis by itself. It is unpredictable what other proteins are required. Given the lack of guidance and the unpredictability of what other proteins are required, excessive experimentation would be required to make and use the claimed invention.

Applicants claim an isolated nucleic acid molecule that hybridizes to SEQ ID NO:3. Isolating DNA fragments using moderate hybridization conditions, does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40 :857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65^0C (page 859, left column, 2^{nd} paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2). Even using stringent hybridization conditions, Fourgoux-Nicol et al isolated a DNA sequence exhibiting less 50% sequence identity with their probe. Given the teachings of the state-of-the-art, Applicants'

hybridization claim is drawn to a multitude of sequences that would not be involved in isoprenoid biosynthesis.

It cannot be predicted by one of skill in the art that nucleic acids that hybridize to SEQ ID NO: 3 under conditions as specified above or nucleic acid sequences that exhibit 85% identity with SEQ ID NO:3 will encode a protein with the same activity as SEQ ID NO:50. Bowie et al (1990, Science 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex (pg 1306, left column). Bowie et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column). The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by McConnell et al (2001, Nature 411 (6838):709-713), who teach that the replacement of a glycine residue located within the START domain of either the PHABULOSA or PHAVOLUTA protein receptor with either an alanine or aspartic acid residue, alters the sterol/lipid binding domain. This change renders the protein constitutively active and therefore creates a dominant mutation which has a drastic alteration in phenotype compared to wild-type *Arabidopsis* plants.

In the absence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by using non-disclosed fragments of SEQ ID NO:3 as probes or by designing primers to undisclosed regions of SEQ ID NO:3 and isolating or amplifying fragments, subcloning the fragments, producing expression vectors and transforming plants therewith, in order to identify those, if any, that when over-expressed produced altered levels of isoprenoid compounds.

Therefore, given the breadth of the claims; the lack of guidance and examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue trial and error experimentation would be required to practice the claimed invention, and therefore the invention is not enabled.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al (1993, NCBI Accession Number X64451).

The claims are drawn to an isolated nucleic acid molecule encoding a protein comprising the amino acid sequence of SEQ ID NO:50, or an isolated nucleic acid molecule that hybridizes to SEQ ID NO:3.

Baker et al disclose a nucleic acid sequence that encodes SEQ ID NO:50. The nucleic acid sequence of Baker et al would also hybridize to SEQ ID NO:3 and as such, Baker et al anticipate the claimed invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claim 8 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 8 is drawn to a seed of the transformed plant. Due to Mendelian inheritance of genes, a single gene introduced into a parent plant would only be transferred at most to half the male gametes and half the female gametes. This translates into only three quarters of the progeny having at least a single copy of the transgene and one quarter of the progeny would not carry a copy of the transgene. Given that there is no indication that there would be any other distinguishable characteristics of the claimed progeny (seeds), it is unclear whether the claimed seeds would be distinguishable from seeds that would occur in nature. See *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 76 USPQ 280 (1948), and *In re Bergy , Coats, and Malik* 195 USPQ 344, (CCPA) 1977. The amendment of the claims to recite that the seeds comprise the construct that was introduced into the parent seed would overcome the rejection.

12. Claims 2, 4-5 and 7-9 are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest an isolated polynucleotide of SEQ ID NO:3 encoding SEQ ID NO:50 and wherein the isolated polynucleotide is operably linked to a nucleic acid sequence

encoding a choroplast transit peptide and operably linked to a promoter, all of which is transformed into a plant and plant seed and a method of producing a transgenic plant having an altered isoprenoid compound level comprising an isolated polynucleotide of SEQ ID NO:3 encoding SEQ ID NO:50 operably linked to a promoter.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 703-305-6997. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Stuart F. Baum Ph.D.

January 12, 2004

AMY J. NELSON, PH.D
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